REMARKS

Claims 1-14 were pending in the present application. Claims 8-14 have been canceled without prejudice. Applicant reserves the right to pursue the subject matter of the canceled claims in one or more related applications.

Claim 1 has been amended to provide the full names for the abbreviations DIM and LTr-1. Support for these amendments can be found in the specification, for example, at paragraph [0018] of U.S. Patent Application Publication No. 2004/0072891 A1, i.e., the publication of the present application. Claim 2 has been amended to correct a typographical error. Applicant has added new claim 15 to encompass an additional embodiment of what Applicant regards as the invention. Specifically, claim 15 has been added to clarify that, in one embodiment, the subject is a human female. Support for this claim can be found in the specification, for example, at paragraph [0059] of U.S. Patent Application Publication No. 2004/0072891 A1.

No new matter has been added by these amendments. Upon entry of these amendments, claims 1-7 and 15 will be pending in the present application.

Applicants respectfully request that the amendments and remarks made herein be entered and fully considered.

Claim Rejections - 35 U.S.C. § 112

Claims 8-14 were rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for administering to a subject an amount of a dietary indole, allegedly does not provide enablement for a method of preventing cervical dysplasia and/or one or more symptoms associated with cervical dysplasia. Without admitting to the propriety of the rejection and in an effort to advance prosecution of the present application, Applicant has canceled claims 8-14. Thus, the rejection has been obviated. Accordingly, Applicant respectfully requests withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Claim Rejections – 35 U.S.C. § 102(a)

Claims 1, 2, 7, 8 and 14 were rejected under 35 U.S.C. § 102(a) as allegedly being anticipated by Liang Jin *et al.*, 1999, Cancer Research 59:3991-3997 (hereinafter

"Liang"). Claims 8 and 14 have been canceled. With respect to claims 1, 2 and 7, Applicant respectfully traverses.

The Examiner contends that Liang researched whether the administration of indole-3-carbinol (I3C) to mice at physiological doses would prevent cervical-vaginal cancer that is promoted by high doses of estrogen. Supplementation with I3C to a diet fed to K14-HPV16 transgenic mice reduced the risk of cervical-vaginal cancer. Supplementation with I3C to a diet fed to nontransgenic FBV/n mice reduced the occurrence of dysplasia. The Examiner also contends that Liang teaches that I3C and its acid condensation product diindolylmethane (DIM) are available as supplements.

> "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

MPEP § 2131.

First, Applicant respectfully submits that Liang does not disclose the treatment of cervical dysplasia, either expressly or inherently. Liang only discusses the prevention of cervical-vaginal cancer or cervical dysplasia. See Liang, for example, title; abstract; page 3993, col. 1, lines 2-4; page 3996, col. 1, lines 2-5; and page 3997, col. 1, lines 32-35. There is nothing in Liang that would indicate that I3C would be useful for the treatment of cervical-vaginal cancer or cervical dysplasia. Notably, in the experiments described in Liang, the mice were implanted subcutaneously with either 0.125 or 0.250 mg per 60-day release pellets of 17β-estradiol prior to commencing supplementation of their diet with I3C. This is clearly a prevention model, not a treatment model, as the mice do not initially have cervical-vaginal cancer or cervical dysplasia. As the Examiner has set forth, with respect to the present invention, "there is a substantial gap between treatment and prevention." Thus, Liang does not disclose a method for treating cervical dysplasia.

Second, Applicant respectfully submits that Liang does not disclose the treatment of cervical dysplasia by administering DIM or LTr-1, either expressly or inherently. The only disclosure in Liang with respect to DIM is its availability as a supplement. See Liang, page 3997, col. 1, lines 18-19. Liang merely discloses that I3C and one of its acid condensation products, i.e., DIM, are available as supplements. This disclosure does not

equate with the administration of DIM to treat cervical dysplasia. Thus, Liang does not disclose a method for treating cervical dysplasia by administering DIM or LTr-1.

Furthermore, Liang's statement (Liang, page 3997, Col. 1, lines 18-19) which does not teach any specific use of DIM is preceded by the words "... condensation of I3C into its active derivatives depends on acids in the stomach (38, 39)." This sentence clearly teaches that there are many derivatives (plural) of I3C. The paragraph as a whole does not teach that DIM is an active derivative of I3C, nor that any single reaction product from I3C would be sufficient to prevent cervical dysplasia. The supporting references cited by Liang confirm this since both Bradfield and Bjeldanes, 1991[1], and Grose and Bjeldanes, 1992[2], clearly teach that I3C converts to a multitude of reaction products and establish that DIM is not distinguished as either the most plentiful (comprising less that 6% of the products produced from I3C under acidic conditions[3]) or the most biologically active[4]. The same authors published an additional reference clearly teaching that indolo[3,2-b]carbazole (ICZ), an I3C condensation product distinct from DIM and LTR-1, much exceeds all other I3C condensation products in biologic activity[5]. Thus in the context of the supporting references cited, Liang provides no teaching that DIM is in fact an active I3C condensation product or an I3C condensation product with relevance to cervical dysplasia.

Accordingly, for the reasons discussed above, Liang does not anticipate the present invention. Applicant respectfully requests that the rejection of claims 1, 2 and 7 under 35 U.S.C. § 102(a) as allegedly being anticipated by Liang be withdrawn.

Claim Rejections – 35 U.S.C. § 103

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[1] Bradfield CA, Bjeldanes LF. Modification of carcinogen metabolism by indolylic autolysis products of Brassica oleraceae. Adv Exp Med Biol. 1991;289:153-63. (Reference #38 from Liang, a copy of which is attached hereto as Reference C21).

[2] Grose KR, Bjeldanes LF. Oligomerization of indole-3-carbinol in aqueous acid. Chem Res Toxicol. 1992 Mar-Apr;5(2):188-93 (Reference #39 from Liang, a copy of which is attached hereto as Reference C22).

[3] *Id* at 188.

[4] See Bradfield at 156.

[5] Bjeldanes LF, Kim JY, Grose KR, Bartholomew JC, Bradfield CA. Aromatic hydrocarbon responsiveness-receptor agonists generated from indole-3-carbinol in vitro and in vivo: comparisons with 2,3,7,8-tetrachlorodibenzo-p-dioxin, Proc Natl Acad Sci U S A. 1991 Nov 1;88(21):9543-7, (a copy of which is attached hereto as Reference C23).

Claims 1-14 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Liang in view of U.S. Patent No. 6,001,868 (hereinafter "Firestone"), and further in view of U.S. Patent No. 5,981,568 (hereinafter "Kunz"). Claims 8-14 have been canceled. With respect to claims 1-7, Applicant respectfully traverses.

Liang has been discussed above. The Examiner notes that Liang does not disclose certain methods of administration and does not disclose microparticles.

The Examiner contends that Firestone teaches bioactive derivatives of I3C, including pharmaceuticals comprising a pharmaceutically acceptable excipient. Firestone also teaches that compositions may be provided in any convenient form including tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, suppositories, etc. The Examiner notes that Firestone also does not disclose microparticles and starch.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art to advance Liang's research by adding more dosage forms to administer DIM locally as well as generally to enhance the effect of the dietary supplement according to the patients' needs.

The Examiner contends that Kunz teaches therapeutic inhibitors of vascular smooth muscle cells. The composition comprise may comprise a diindoloalkaloid as defined in Kunz. The Examiner alleges that DIM is considered a diindoloalkaloid because it contains nitrogen. The compositions may contain starch, be in the form of a microparticle, and can be administered through a variety of delivery routes, including oral, parenteral, rectal and transdermal.

The Examiner concludes that it would have been obvious to one of ordinary skill in the art at the time the invention was made to make the composition comprising DIM in the form of microparticles and to admininster DIM as a suppository, or in a topical, transdermal or oral form.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

> Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either explicitly or implicitly in the references themselves or in the knowledge generally available to one of ordinary skill in the art.
>
> Obviousness does not require absolute predictability, however, at least some degree of predictability is required. Evidence showing there was no reasonable expectation of success may support a conclusion of nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA 1976).
>
> To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

MPEP §§ 2143 – 2143.03.

First, Liang does not provide a suggestion or motivation for the treatment of cervical dysplasia by administering DIM or LTr-1. As discussed above, Liang only discusses the prevention of cervical-vaginal cancer and cervical dysplasia using I3C. There is nothing in Liang that would suggest or provide a motivation for a method of treatment of cervical dysplasia with I3C, much less with DIM or LTr-1. As discussed above, Liang merely discloses that I3C and one of its acid condensation products, i.e., DIM, are available as supplements. Liang further discloses that condensation of I3C results in multiple active derivatives. See Liang, page 3997, col. 1, lines 15-17 (emphasis added). There is no teaching or suggestion in Liang that DIM is the active derivative, or an active derivative, that is useful for preventing cervical dysplasia. In fact, the related references suggest that active derivates of I3C other than DIM are responsible for the biologic activity associated with oral use of I3C, and ICZ is the most most potent I3C related product (see previous discussion and Footnote 5).

Firestone does not remedy the deficiencies of Liang. The Examiner has used Firestone for teaching additional dosage forms for DIM. Without admitting to the propriety of the combination with Liang, Applicant respectfully submits that Firestone does not teach the treatment of cervical dysplasia nor does Firestone teach that DIM would be useful for the treatment of cervical dysplasia. With respect to the latter, Firestone provides a useful summary of I3C and its derivatives. See Firestone, col. 2, lines 27-44. Firestone teaches that I3C is converted into several natural indole derivatives, including DIM and indolo[3,2-b]carbazole (ICZ), with biological activities. See id. Significantly, Firestone teaches that

ICZ is a potent inhibitor of several estrogen-dependent processes. See id., col. 2, lines 48-54. Moreover, Firestone teaches that I3C itself, and not its acid breakdown products, is a potent anti-tumor agent. See id. col. 3, lines 13-14. An object of the invention of Firestone is to obtain stable derivatives of I3C, other than its natural gastric acid metabolites. See id., col. 3, lines 13-59. These teachings in Firestone do not provide a suggestion or motivation that DIM (or LTr-1) would be useful for the treatment of cervical dysplasia. If anything, these teachings of Firestone teach away from the present invention.

Kunz does not remedy the deficiencies of Liang and/or Firestone. The Examiner has used Kunz for the teachings of formulating diindoloalkaloids with starch or as microparticles and admistering these compounds through a variety of administration routes (contending that DIM is considered to be a diindoloalkaloid). Without addressing the propriety of the Examiner's contention that DIM is a diindoloalkaloid, Applicant respectfully submits that Kunz does not teach, suggest or provide a motivation for using DIM to treat cervical dysplasia as Kunz does not discuss cervical dysplasia at all.

Thus, Liang, either alone or in combination with Firestone and/or Kunz, does not provide a suggestion or motivation for the present invention.

Second, Liang, either alone or in combination with Firestone and/or Kunz, does not provide a reasonable expectation of success for the present invention. As discussed above, none of the cited references provide any guidance as to what active derivative of I3C may be responsible for its activity in preventing cervical-vaginal cancer and/or cervical dysplasia. Without knowing which derivative among the many active derivatives is responsible for the treatment of a particular disease or condition, there cannot be a reasonable expectation of success based on the teachings of the cited references. As discussed, ICZ is known in the related art to have more biologic activity than DIM or LTR-1 (see footnote 5 above), adding further doubt as to the expectation of success using DIM or LTR-1 administered as individual agents. Furthermore, as discussed above, the cited references do not provide a teaching, suggestion or motivation for the treatment of cervical dysplasia. As there is a substantial gap between the treatment of cervical dysplasia and its prevention, there cannot be a reasonable expectation of success based on the teachings of the cited references.

Finally, Liang, either alone or in combination with Firestone and/or Kunz, does not teach all of the claim limitations. Specifically, none of the cited references teach,

suggest or provide a motivation for a method of treating cervical dysplasia. The cited references only teach I3C for the prevention of cervical-vaginal cancer and cervical dysplasia.

Accordingly, for the above reasons, Applicant respectfully submits that a *prima facie* case of obviousness is improper. Applicant respectfully requests that the rejection of claims 1-7 under 35 U.S.C. § 103(a) as allegedly being obvious over Liang in view of Firestone, and further in view of Kunz, be withdrawn.

CONCLUSION

Applicant respectfully requests that the above-made amendments and remarks be entered and made of record in the file history of the instant application.

Respectfully submitted,

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